UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/865,579	05/29/2001	Toshiki Taya	9558-003-27	3666

7590 11/28/2003

Supervisor, Patent Prosecution Services
PIPER MARBURY RUDNICK & WOLFE LLP
1200 Nineteenth Street, N.W.
Washington, DC 20036-2412

EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 11/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/865,579	TAYA ET AL.	
	Examiner	Art Unit	
	Julie C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 9-13* is/are pending in the application.

4a) Of the above claim(s) *1-4* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. This action is written in response to applicant's correspondence submitted 8/13/03. Claims 5-8 have been canceled and claims 9-13 have been added. Claims 1-4 and 9-13 are pending. Claims 1-4 are withdrawn from prosecution. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

2. The IDS filed 10/3/03 has not been considered as the references were not received with the IDS (It is noted in the transmittal that the references were not sent when the 1449 was sent to this application). The information disclosure statement filed 10/3/03 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the references were not mailed with the proper filing of the 1449. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

3. This application contains claims 1-4 drawn to an invention nonelected with traverse in the paper filed 11/26/02. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 13 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

In claim 13, the new limitation wherein SEQ ID NO: 20 is used as a detection probe labeled with an intercalator fluorescent dye appears to represent new matter. No specific basis for this limitation was identified in the specification, nor did a review of the specification by the examiner find any basis for the limitation. The specification and claims as originally filed teach methods which utilize SEQ ID NO: 20 as a first or second primer, but not as a detection probe which is complementary to a portion of the RNA product transcribed from the double-stranded cDNA product and labeled with an intercalator dye. Since no basis has been identified, the claims are rejected as incorporating new matter.

6. Claims 9-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 9, part (b), the phrase "the RNA derived from the mecA gene" lacks proper antecedent basis in the claim because the claim does not previously refer to an RNA derived from a mecA gene, thus it is unclear what RNA this limitation of the claim is referring to. Claims 10-13 depend from claim 9 and are indefinite over this same recitation.

Claim Rejections - 35 USC § 103

7. Claims 9 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bekkaoui *et al.* (US 6136533) in view of Ryffel *et al.* (Gene, 94 (1999) 137-138).

Bekkaoui *et al.* teach a detection method employing an RNA amplification process which comprises the steps of:

(a) preparing a reaction mixture comprising:

a sample;

a first oligonucleotide primer (Col. 13, lines 15-16);

a second oligonucleotide primer; wherein said second oligonucleotide primer comprises and RNA polymerase promoter sequence at the 5'region (Col. 13, lines 16-17);

an enzyme or a mixture of enzymes having (i) RNA-dependent DNA polymerase activity (Col. 13, line 18), (ii) ribonuclease activity that hydrolyzes RNA of an RNA-DNA hybrid without hydrolyzing single-stranded and double-stranded RNA or DNA (Col. 13, lines 20-22),

(iii) DNA-dependent DNA polymerase activity (Col. 13, lines 19-20); and (iv) DNA-dependent RNA polymerase activity (Col. 13, lines 17-18);

(b) incubating said reaction mixture under conditions that allow the formation of a double-stranded cDNA product from the RNA derived from the template DNA (Col. 13, lines 25-45); and

(c) detecting the RNA product transcribed from the double-stranded cDNA product (Col. 15, lines 4-34).

Bekkaoui *et al.* also teach methods wherein the mecA gene is used as a target for the detection of the presence of methicillin resistant Staphylococcus aureus (Col. 33-35). Bekkaoui *et al.* teach a probe useful for such detection, namely their SEQ ID NO: 4. This sequence taught by Bekkaoui *et al.* overlaps with instant SEQ ID NO: 20 and SEQ ID NO: 21. Particularly, instant SEQ ID NO: 20 falls entirely within the region of the mecA gene that the probe taught by Bekkaoui *et al.* Bekkaoui *et al.* further provide guidance as to how to select probes useful for the methods disclosed in their patent (Col. 6). Bekkaoui *et al.* do not exemplify the RNA amplification process for the detection of the mecA gene, nor do they teach primers that comprise portions of SEQ ID NO: 18, 19, 20, 21, 22, 23, 24, or 25.

Ryffel *et al.* provide the full length sequence of the mecA gene isolated from three different methicillin resistant Staphylococci. Ryffel *et al.* specifically point out the regions where the sequence of the mecA gene is identical between the three versions of the gene, and the regions that differ between them. Each of nucleic acid primers SEQ ID NO: 18-25 disclosed herein is contained within the sequence taught by Ryffel *et al.* For example, instant SEQ ID NO: 18 is identical to nucleotides 749-776 of the sequence taught by Ryffel et al, and instant SEQ ID

NO: 19 is identical to the complement of nucleotides 1229-1242 of the sequence taught by Ryffel *et al.* Further, each of the probes recited in claims 11 and 13 are contained within the sequence taught by Ryffel *et al.* For example, instant SEQ ID NO: 27 falls within the region between SEQ ID NO: 18 and SEQ ID NO: 19, as it is the complement of nucleotides 1065-1103 of the sequence taught by Ryffel *et al.*

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the RNA amplification method taught by Bekkaoui *et al.* for the detection of the mecA gene in a sample. The ordinary practitioner would have been so motivated by the teachings of Bekkaoui *et al.* of the RNA amplification method and the exemplification of the mecA gene as a marker of MRSA in a sample. The use of the method taught by Bekkaoui *et al.* for the detection of the mecA gene in a sample would necessarily have required the selection of primers from within the mecA gene. In light of the teachings of Ryffel *et al.*, who provide the full length sequence of the mecA gene from different MRSA, it would have been prima facie obvious to one of ordinary skill in the art to have selected any of the primers disclosed as SEQ ID NO: 18-25, or portions of these sequences. The ordinary practitioner would have been motivated to select these primers because they are each within a region of the mecA gene that is conserved among the different versions of the mecA gene. Selection of primers in such regions would increase the likelihood of detection of each of the three versions of the mecA gene. Thus, in light of the teachings of the prior art, the instant invention is *prima facie* obvious.

With regard to claim 11, this limitation is only relevant in the case wherein the first oligonucleotide primer comprises the RNA polymerase promoter sequence, but this is not the

embodiment of claim 9 taught by Bekkaoui *et al.* in view of Ryffel *et al.* Neither claim 9 nor claim 11 require the presence of the cleaving oligonucleotide probe, in these claims this limitation is optional only in the case where the first primer has the promoter sequence. The teachings of Bekkaoui *et al.* in view of Ryffel *et al.* apply to claim 11 because the embodiment being rejected therein is the optional embodiment that does not require the cleaving oligonucleotide probe.

Alternatively, however, it is noted that a reaction mixture that comprises a cleaving probe is necessarily produced in the methods taught by Bekkaoui *et al.* in that the actual process of extending the segment when the primer hybridizes to an RNA necessarily creates a probe that is subsequently cleaved (or a cleavage probe). For example, the use of a primer pair comprising SEQ ID NO: 18 and SEQ ID NO: 20, or portions thereof, would necessarily result in the production of a DNA segment that comprises SEQ ID NO: 27 as the primers are extended during the reaction. Such a DNA segment is considered a "cleavage probe" insofar as it would subsequently be cleaved by the degradation enzyme taught by Bekkaoui *et al.* Thus, even if the claim required the presence of the cleavage probes, the teachings of Bekkaoui *et al.* necessarily would meet this limitation.

8. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bekkaoui *et al.* in view of Ryffel *et al.* as applied to claims 9 and 11 above, and further in view of Davey *et al.* (US 5554517).

The teachings of Bekkaoui *et al.* in view of Ryffel *et al.* are applied to claim 10 as they are applied in the previous rejection. Bekkaoui *et al.* in view of Ryffel *et al.* do not provide a

wherein said RNA polymerase promoter sequence comprises the sequence recited in SEQ ID NO: 30.

Davey *et al.* teach a nucleic acid amplification process that is substantially identical to the process being employed by Bekkaoui *et al.* (see Figure 1 of Davey *et al.*, for example), and Davey *et al.* particularly teach the use of a promoter sequence identical to SEQ ID NO: 30 linked to the second primer (see Col. 6, lines 46-47). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the promoter sequence taught by Davey *et al.* in the methods taught by Bekkaoui *et al.* in view of Ryffel *et al.* One would have been motivated to utilize this sequence because it was a widely used promoter sequence, and Davey *et al.* specifically teach and exemplify the use of this sequence as a portion of a promoter-primer as is used by Bekkaoui *et al.*

9. Claims 11, 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bekkaoui *et al.* in view of Ryffel *et al.* as applied to claims 9 and 11 above, and further in view of Ishiguro *et al.* (Nucleic Acids Research, 1996, Vol. 24, No. 24, pages 4992-4997).

The teachings of Bekkaoui *et al.* in view of Ryffel *et al.* are applied to claims 11, 12, and 13 as they are applied in the previous rejection. Bekkaoui *et al.* in view of Ryffel *et al.* do not provide a method which includes an oligonucleotide probe labeled with an intercalator fluorescent dye wherein the probe is complementary to the RNA transcription product and wherein the binding of the probe to said RNA transcription product results in a change of the fluorescent property relative to that of a situation where a complex formation is absent, then measuring the fluorescence intensity of the reaction solution.

Ishiguro *et al.* teach methods wherein a probe labeled with an intercalator fluorescent dye is included in an *in vitro* transcription application in order to provide an easy and specific homogeneous method to detect a nucleic acid sequence (p. 4992). Ishiguro *et al.* teach that "The present success of the applicability of the probe to real-time monitoring of the in vitro transcription showed that YO-linked DNA probe can be a powerful tool with which to construct a new methodology to study the dynamics of gene expression, and also to provide a more practical way of detecting and quantifying a target sequence in a clinical specimen specifically in a homogeneous format (p. 4997)." Thus, in light of the teachings of Ishiguro *et al.*, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included an oligonucleotide probe labeled with an intercalator fluorescent dye wherein the probe is complementary to the RNA transcription product in the method taught by Bekkaoui *et al.* in view of Ryffel *et al.* The ordinary practitioner would have been motivated to include such a probe in order to provide a practical way of detecting and quantifying target sequence in a clinical specimen in a homogeneous format, as is taught by Ishiguro *et al.* Furthermore, the ordinary practitioner would have been motivated to select a probe sequence from within the nucleotide sequence taught by Ryffel *et al.*, especially a probe comprising instant SEQ ID NO: 20, since Ryffel *et al.* specifically exemplify that this is an effective target region for detection of the mecA gene.

Futhermore, it is noted with regard to claims 9 and 11 that the detection probe taught by Ishiguro *et al.* would also function as a "cleavage probe" as recited in claims 9 and 11, as if such a probe hybridized with the RNA template, the probe would be useful to induce cleavage of the RNA portion of the template. Each of the probes recited in claim 13 are contained within the

sequence taught by Ryffel *et al.* For example, instant SEQ ID NO: 27 falls within the region between SEQ ID NO: 18 and SEQ ID NO: 19, as it is the complement of nucleotides 1065-1103 of the sequence taught by Ryffel *et al.* Thus, it would have been prima facie obvious to one of ordinary skill in the art to have selected any of these interior sequences for use as a probe with the methods taught by Bekkaoui *et al.* in view of Ryffel *et al.*

Response to Remarks

New grounds of rejection are set forth to address the newly filed claims.

Applicant's arguments with regard to the combination of Bekkaoui *et al.* and Ryffel *et al.* are addressed insofar as they are relevant to the newly filed claims.

Applicant points out that Bekkaoui does not disclose the primer combination claimed in the present invention, a point with which the examiner agrees, as is noted in the 103 rejection, and that Ryffel discloses the full length sequence of the mecA gene. This is also undisputed. In addition, however, it is noted that Ryffel *et al.* align the genes from three species It is the combination of the references, given the guidance in Bekkaoui *et al.* of a general method for the detection of MRSA via the detection of the mecA gene, and the provision of the sequences by Ryffel *et al.* that provides the instant invention. The selection of any primers or probes from within conserved regions would have been obvious to one of ordinary skill in the art in order to practice the methods taught by Bekkaoui *et al.* for the detection of MRSA. These would all have been considered functional equivalents. In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, however, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed oligonucleotides simply represent structural homologues of the full length disclosed mecA sequence concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, for example for use in detection methods, the claimed methods utilizing the disclosed primers and probes are *prima facie* obvious over the cited references.

Applicant further argues that neither Bekkaoui nor Ryffel teaches or suggests the use of a cleaving probe. However, this is not persuasive, as is addressed in the rejections. First, it is noted that applicant is arguing a limitation that is not expressly required in the instant claims because the recitation of the limitation is a conditional recitation wherein it is only required if the "first" primer is the primer with the promoter attached. In the instant rejections, the "second" primer has the promoter, and thus, the limitation is not required. Nonetheless, the limitation is addressed in the rejections in the interest of compact prosecution.

Applicant points out differences in the use between SEQ ID NO: 4 of Bekkaoui *et al.* and instant SEQ ID NO: 20 or 21. This is granted. Primers which initiate synthesis are taught by Bekkaoui *et al.* as well, as is cited in the rejection. The examiner is relying on SEQ ID NO: 4 of Bekkaoui *et al.* merely to demonstrate that Bekkaoui *et al.* utilized this common region of the mecA gene as a target for detection methods, thus demonstrating that the mecA gene is useful for such methods.

Applicant's further argue that the full length sequence of a gene does not automatically provide primer/probe sequences for a particular application. Nor did the examiner argue that this is the case. Bekkaoui *et al.* teach a method which utilizes such primers. Furthermore, Ryffel *et al.* do not simply provide a single full length sequence, they provide an alignment of three sequences from three different species of MRSA, which would provide the practitioner with a means for selecting oligonucleotides for the practice of the methods taught by Bekkaoui *et al.* Applicant states that SEQ ID NO: 19, 21, 23, 24 and 25 are within regions that are not conserved among different mecA genes. However, it is not clear how applicant comes to this conclusion, when based on the figure provided by Ryffel *et al.* these primers are all within regions that are taught by Ryffel *et al.* each of these primers are within regions that are common to all three given sequences. Particularly, SEQ ID NO: 19 is the complement of nucleotides 1229-1242 of the sequences taught by Ryffel *et al.*, SEQ ID NO: 21 is the complement of nucleotides 1109-1128 of the sequences taught by Ryffel *et al.*, SEQ ID NO: 23 is the complement of nucleotides 1296-1315 of the sequences taught by Ryffel *et al.*, SEQ ID NO: 24 is the complement of nucleotides 1363-1382 of the sequences taught by Ryffel *et al.*, and SEQ ID NO: 25 is identical to nucleotides 1121-1142 of the sequences taught by Ryffel *et al.* Each of these sequence is entirely conserved among the three versions of the mecA gene taught by Ryffel *et al.* As noted previously, they would all be expected to function as equivalents in methods for detection of the gene. Thus, given the methodology provided by Bekkaoui *et al.* and the teachings provided by Ryffel *et al.* the rejections are maintained and applied to the newly added claims.

Conclusion

10. No claims are allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Switzer whose telephone number is 703 306 5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703 308 1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703 305 3592 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308 0196.

Juliet C Switzer
Art Unit 1634

November 18, 2003

W Gary Jones
Supervisory Patent Examiner
Technology Center 1600